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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,179	07/02/2003	Roland Kreutzer	A2038-706120	5239

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
05/01/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/612,179	KREUTZER ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6-9 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6-9 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/16/08, 9/17/08, 12/23/08 and 4/3/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Claim Rejections - 35 USC § 112

Claims 4 and 6-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are directed to isolated oligoribonucleotide having a double stranded structure (dsRNA) consisting of two separate non-linked complementary RNA strands, wherein the dsRNA is 21 nucleotides in length.

Applicants' remarks filed April 22, 2005 state that support for the amendments to the claims can be found throughout the specification, such as at page 4. A review of the specification, and particularly page 4, does not reveal support for where the various claim amendments are found.

The specification discloses on page 4 that the dsRNA of the instant invention has 10 to 1,000, preferably 15 to 49, base pairs. Page 4 further makes reference to "complementary region I", which on page 2 is defined as being complementary to the target gene.

The portion of page 4 referred to in the remarks (page 4, line 26) refers to two separate RNA strands, however this disclosure is in the context of "a region II which is complementary within the double stranded structure". There is no disclosure within the specification of the relationship between complementary region I and this "region II" such that the skilled artisan would recognize that this disclosure of separate RNA strands refers to the preferred 15-49 bp dsRNA.

In the remarks of 12/23/08 Applicants argue that *Wertheim* is not relevant, because it was concerned with claiming ranges while the instant claims are directed to a single length, but rely on this case to argue that dsRNAs longer than 30 nucleotides are not a "different invention" in the sense of *In re Wertheim*.

Applicants are correct that the claims no longer recite a range, therefore Wertheim does not have to be considered and the issue of whether a dsRNA of 21 nucleotides is a different invention is moot.

The issue at hand is the support for a claim to a specific embodiment based on a generic disclosure. The instant specification generically discloses dsRNAs that can be 15-49 bases in length.

While the working examples do disclose use of a single 21 nucleotide RNA, the strands of this RNA are connected by a non-nucleotide linker; therefore RNA of the recited length appears only in the context of covalently linked strands. The specification does not contemplate a limitation wherein the dsRNA is both 21 nucleotides in length and consists of separate non-linked strands and hence does not provide support for such.

While applicants assert the specification, plainly on its face, shows possession of 21 nucleotide dsRNAs lacking a linkage, they do not point where this embodiment appears. applicants state that example 2 provides the support for the length of 21 base pairs, but if one accepts applicants' assertion that the generic disclosure of their compounds embraces embodiments of "15-49 and not linked" as well as "15-49 and linked", it is clear that the specific embodiment of example 2 is "21 and linked". Applicants argue the sentence quoted in the office action is an observation relating to the specific embodiment described at Example 2 that is not a limitation imposed on the specification as a whole. However, this is the embodiment being relied upon as providing support for the specific embodiment of dsRNAs of 21 nucleotides. By claiming the embodiment "21 and not linked", applicant is excluding their only disclosure of an embodiment of 21 nucleotides.

Claim Rejections - 35 USC § 102 and 103

The instant invention is drawn to an isolated oligoribonucleotide consisting of two separate non-linked RNA strands of 21 nucleotides wherein the first strand is complementary to a mammalian target and the second strand is complementary to the first strand. In specific embodiments, the target gene is a mammalian gene, one strand of the dsRNA is fully complementary to the target gene, the two RNA strands are fully complementary to each other and the target is a primary or processed RNA transcript.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The later-filed application must

be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The instant application does not receive the benefit of 09/889,802 or earlier applications because claims 4 and 6-9 of the instant application are not supported by the specification and claims of these applications, as demonstrated in the new matter rejection above. The parent applications do not disclose a limitation wherein the dsRNA contains separate non-linked strands and is 21 nucleotides in length. Thus, the effective filing date is determined to be that of the instant application, July 2, 2003.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4 and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir et al. (Nature 2001, of record).

Elbashir et al. disclose 21-nucleotide siRNA duplexes that are transfected into mammalian cells to specifically suppress expression of endogenous and heterologous genes in different mammalian cell lines (see page 494). Elbashir et al. also disclose duplexes comprising deoxythymidine, which is a modified ribonucleotide to enhance nuclease resistance (see pages 495 and 496).

Thus, Elbashir et al. disclose all limitations of and anticipate claims 4 and 6-9.

Claims 4 and 6-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (WO 02/44321, of record).

Tuschl et al. disclose dsRNA consisting of two separate RNA strands of 19-25 nucleotides, preferably 21 nucleotides, which are capable of mediating RNAi, including in mammalian cells (see pages 3-4 and page 8, lines 4-25). One strand of the duplex is preferably 100% complementary to the target and siRNAs containing at least one modified nucleotide analog, for example a 2'-O-methyl sugar modification of a phosphorothioate are especially preferred (see pages 6 and 46). Tuschl et al. also

disclose (see page 44) that the dsRNA of their invention can be 21 nucleotide siRNA duplexes with blunt ends, which are two strands fully complementary to each other.

Therefore, Tuschl et al. disclose all limitations of and anticipate claims 26-33 and 35.

Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (WO 94/01550, of record).

The claims are directed to a dsRNA 21 nucleotides in length wherein a linker connects the two complementary strands. The linker may be a covalent bond and one strand of the RNA may be fully complementary to a mammalian target gene.

Agrawal et al. teach self-stabilized oligonucleotides useful for antisense therapeutics that comprise a target hybridizing region and a self-complementary region. On page 9, line 30 through page 10 line 1 Agrawal et al. disclose that the target hybridizing region is complementary to a nucleic acid sequence from a variety of sources and is from 8-50 nucleotides in length. On page 15, line 26 through page 17, line 12 Agrawal et al. disclose that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region, the hybridizing region and the self-complementary region can be linked by a polyethylene glycol linker, which is a chemical linker that forms a covalent bond. Agrawal et al. do not explicitly disclose an embodiment wherein the RNA is 21 nucleotides in length but it would be obvious to one of ordinary skill in the art to make such an oligonucleotide. One of ordinary skill in the art would recognize that producing an oligonucleotide of 21 nucleotides is a matter of design choice based on the disclosure in Agrawal et al. that the self-stabilized

oligonucleotides can be up to 50 nucleotides in length and the target hybridizing and self-complementary regions can be of identical length and the recognition that antisense oligonucleotides are generally around 17-25 nucleotides in length. One could predictably make oligonucleotides of the recited length because chemical synthesis of oligonucleotides is routine in the art.

Thus, claims 16-18 would have been obvious, as a whole, at the time the invention was made.

New Rejection

Claims 4 and 6-9 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Crooke (US 6,107,094, of record).

Crooke discloses oligomeric compounds for the purposes of inhibiting gene expression. One embodiment of these compounds is found in example 27-a at column 50 (see also table 1), which disclose fully complementary double stranded RNAs 18 and 20 nucleotides in length targeted to either Ha-ras or C-raf. These sequences are complementary to less than the full length of an RNA transcript and do not comprise a full length transcript. Crooke does not explicitly disclose that these RNAs will inhibit gene expression but since the prior art meets all structural limitations of the claims it would, absent evidence to the contrary, be expected to inhibit gene expression. At column 14, Crooke discloses that his oligonucleotides are preferably from 15-25 nucleotides in length. Given the small size of the preferred genus of compounds, the

skilled artisan would immediately envisage compounds of each length from 15-25 nucleotides, including 21 nucleotides.

In the alternative, because Crooke teaches double stranded oligomeric compounds of 20 nucleotides in length that are useful as artificial enzyme substrates and further teaches that the preferred length of his oligomeric compounds is 15-25 nucleotides, one of ordinary skill in the art would recognize production of an artificial substrate of 21 nucleotides to be a matter of design choice.

Thus, Crooke anticipates or renders obvious claims 4 and 6-9.

Response to Arguments

Applicants traverse the previously applied 102 rejections by noting these references are not available as prior art. These arguments are not persuasive because the priority date for claims 4 and 6-9 remains July 2, 2003.

Applicants traverse the 103 rejection over Agrawal by asserting this reference is clearly about oligonucleotides having a hairpin structure and one of ordinary skill in the art would not read Agrawal et al. to suggest an oligoribonucleotide consisting of two separate complementary oligoribonucleotide strands (dsRNA). Applicants further argue that Agrawal et al. teachings require that the self-complementary region fold back and hybridize with itself, not with the target hybridizing region. Based on this interpretation applicants conclude that the non-nucleotide linker envisioned by Agrawal would not bridge a duplex structure, but a structure like that shown on page 10 of the remarks.

This is not persuasive because the interpretation applicants give to the reference's teachings is not consistent with Agrawal et al. itself. Agrawal et al. teach that the self-complementary region and the target hybridizing region can be connected by a non-nucleotide linker but does not teach the self complementary region does not hybridize with the target complementary region. Figure 1 shows in cartoon form the self-complementary region, represented by circles, base-pairing with the target hybridizing region represented by squares. Further, Agrawal et al. explicitly teach that "the intramolecular base pairing can be so extensive as to involve every nucleotide of the oligonucleotide", which would not be possible if the self-complementary region was unable to hybridize with the target hybridizing region.

With regard to the newly applied rejection, this reference was previously dropped when the claims were limited to dsRNAs 21 nucleotides in length. However, upon further consideration of the disclosure of the reference it is the examiner's position that Crooke does constitute prior art for the reasons set forth in the rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is (571)272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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